Determinants of haemodialyser performance and the potential effect on clinical outcome

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Abstract
The performance of a dialyser is determined by several factors. Many of these factors relate to the dialyser membrane, including mean pore size, pore size distribution, wall thickness, surface area, and adsorptivity. In this article, several of these factors are reviewed. The potential impact of these factors on the clinical outcome of chronic haemodialysis patients is also discussed.

Keywords: convection; dialyser; flux; haemodialysis; membrane

Fundamental properties of haemodialyser membranes
A dialyser used for HD has a 2-fold purpose. First, its membrane acts as a semi-permeable barrier for the transfer of solutes primarily from blood to dialysate, but also in the opposite direction. Removal of low molecular weight uraemic toxins occurs almost exclusively by diffusion, while convection and adsorption generally assume an important role in the removal of larger compounds such as peptides and proteins. The second basis function of a haemodialyser is the ultrafiltration of plasma water.

Introduction
When selecting a dialyser for a chronic haemodialysis (HD) patient, a clinician must consider several factors, including performance, biocompatibility, water permeability (flux), mode of sterilization, and cost. With respect to performance, the most logical manner to assess the solute removal capabilities of a dialyser is to use the depuration properties of the native kidney as a benchmark. The purpose of this article is to review the several important dialyser characteristics that have the greatest impact on its solute removal performance over a wide spectrum of uraemic toxins. Specifically, mean pore size, pore size distribution, wall thickness, flux and adsorptivity are discussed. The potential impact of some of these factors on the clinical outcome of chronic HD patients is also highlighted.

Dialyser membrane water permeability
A hollow fiber dialyser membrane can be modelled as having straight cylindrical pores, all of the same radius (r) and all with a directionality perpendicular to the flow of blood and dialysate [1]. As discussed below, this model does not exactly replicate a clinical dialyser but is useful from a quantitative perspective nevertheless. The major determinants of plasma ultrafiltrate flow rate through the pores are the number of pores (i.e. number per unit of membrane surface area), transmembrane pressure and pore size. However, this rate of ultrafiltrate flow is actually dependent on the fourth-power of the pore radius (i.e. r⁴). As such, the membrane characteristic that most directly influences water permeability is mean pore size.

Water permeability has traditionally been used to categorize haemodialysers. In the past, this was largely driven by the existence of HD machines, both with and without ultrafiltration control mechanisms, and the limitation that only dialysers of relatively low water permeability be used in conjunction with non-ultrafiltration control machines. However, the vast majority of machines in the market now have

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ultrafiltration control mechanisms so a more relevant dialyser classification scheme is one based on both water permeability and solute removal properties [2]. Such a scheme is proposed in Table 1. Although both conventional and high efficiency classes are characterized by low water permeability, dialysers in the latter category have higher surface areas and are typically employed in high-flow rate settings to maximize small solute clearances [3]. The larger mean pore sizes of the mid-flux and high-flux categories generally lead to enhanced removal of intermediate and large-sized uraemic compounds.

### Haemodialyser membrane diffusive permeability

Membrane wall thickness is one important determinant of diffusive transport [4]. The relatively thin walled structure of cellulosic membranes (usually 6–15 μm) is largely responsible for their particular suitability in the setting of diffusive HD. The other major determinant of dialyser membrane diffusive transport is porosity, also known as pore density. Based on the cylindrical pore model described above, membrane porosity is directly proportional to both the number of pores and the square of the pore radius \( r^2 \). Therefore, the smaller dependence of membrane porosity on pore size, relative to the case of water permeability, implies a relatively greater importance of pore number in determining diffusive permeability. That the major determinants of flux \( J \) and diffusive permeability (number of pores, \( r^2 \) and wall thickness) differ so significantly implies that the two properties can be independent of one another for a particular haemodialysis membrane [5]. Such is the case for cellulosic high-efficiency dialysers, which typically have very high diffusive permeability values for small solutes but low water permeability.

### Pore size distribution effects on dialyser membrane properties

A membrane represented by the cylindrical pore model described above deviates from an actual membrane used for clinical HD in that the latter actually has a distribution of pore sizes. Ronco et al. [6] have recently discussed the manner in which pore size distribution may differ between HD membranes and the manner in which this distribution influences a membrane’s sieving properties (Figure 1). The membrane represented by curve A has a large number of relatively small pores, while the membrane represented by curve B has a large number of relatively large pores. Based on the relatively narrow pore size distributions, the solute sieving coefficient vs molecular weight profile for both membranes has the desirable sharp cut-off, similar to that of the native kidney. However, the molecular weight cut-off for membrane A (~10 kDa) is consistent with a high-efficiency membrane, while that of membrane B (~60 kDa) is consistent with a high-flux membrane. In addition, primarily due to the large number of pores, both membranes would be expected to demonstrate favourable diffusive transport properties. On the other hand, membrane C exhibits a pore size distribution that is unfavourable from both a diffusive transport and sieving perspective. The relatively small number of pores accounts for the poor diffusive properties. In addition, the broad distribution of pores explains not only the ‘early’ drop-off in sieving coefficient at relatively low molecular weight, but also the ‘tail’ effect at high molecular weight. This latter phenomenon is highly undesirable as it may lead to unacceptably high albumin losses across the membrane.

### Dialyser membrane properties influencing non-diffusive removal

Larger molecular weight uraemic toxins, particularly peptides and proteins, are cleared inefficiently by diffusion during HD. Solutes of this type may be removed primarily by convection or adsorption, or a combination thereof [7–9]. Ultrafiltration rate and the dialyser membrane’s sieving properties are the two most important determinants of convective solute removal [10]. As noted by several investigators [11,12], typical clinical use of a high-flux dialyser dictates that the net ultrafiltration rate (i.e. the rate of patient weight loss due to due net plasma water removal) is not equivalent to the absolute ultrafiltration rate in the dialyser. In fact, the rate of filtration from blood to dialysate in the proximal portion of the dialyser and the rate of ‘backfiltration’ from dialysate to blood in the distal part of the dialyser is significantly higher than the net ultrafiltration rate. This internal filtration mechanism, physiologically analogous to Starling’s flow, contributes significantly to overall convective solute removal by a high-flux dialyser. In fact, attempts

<table>
<thead>
<tr>
<th>Class</th>
<th>Surface area</th>
<th>( K_{\text{UF}} ) (ml/h/mmHg)</th>
<th>Urea clearance</th>
<th>( \beta/2\text{M} ) clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td>&lt;1.5 m²</td>
<td>&lt;12</td>
<td>Moderate</td>
<td>Negligible</td>
</tr>
<tr>
<td>High efficiency</td>
<td>&gt;1.5 m²</td>
<td>&lt;12</td>
<td>High</td>
<td>Negligible</td>
</tr>
<tr>
<td>Mid-flux</td>
<td>Variable</td>
<td>12–30</td>
<td>Variable</td>
<td>Moderate</td>
</tr>
<tr>
<td>High-flux</td>
<td>Variable</td>
<td>&gt;30</td>
<td>Variable</td>
<td>High</td>
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to enhance quantitatively the removal of middle molecules by this mechanism, either by manipulations in blood compartment or dialysate-side pressure, have recently been described [13–15].

Adsorption (membrane binding) is another mechanism by which hydrophobic compounds like peptides and proteins may be removed during HD. Although adsorption during HD is a relatively poorly understood phenomenon, certain membrane characteristics play an important role. First, adsorption primarily occurs within the pore structure of the membrane rather than at the nominal surface contacting the blood only [16]. Therefore, the open pore structure of high-flux membranes affords more adsorptive potential than do low-flux counterparts. Secondly, synthetic membranes, many of which are fundamentally hydrophobic, generally are much more adsorptive than hydrophilic cellulose membranes [17].

Effect of dialyser membrane flux on mortality in chronic haemodialysis patients

Several recent retrospective studies have assessed the relationship between membrane type and mortality in the chronic HD population. However, in some of these studies, membrane composition and flux have been covariates. For example, using the United States Renal Data Systems (USRDS) database, Hakim et al. [18] retrospectively analysed the effect of membrane on mortality in ~2400 patients. These patients were a randomly selected cohort of HD patients who had been on HD for at least 1 year and were receiving treatment in 1990. For analysis purposes, dialysis membranes were categorized according only to polymeric composition into unsubstituted cellulose, substituted cellulose (‘semisynthetic’), and synthetic classes. Therefore, the unsubstituted cellulose class was homogeneous with respect to flux (low permeability), while the flux of the dialysers in the other two groups could theoretically vary. The Cox model was used to determine the relative risk of death for each membrane group, with the unsubstituted cellulose group having a reference value of 1.0. All results were adjusted for a battery of clinical parameters, such as demographic characteristics, cause of end-stage renal disease, major comorbidities and serum albumin concentration. Adjustments were also made sequentially for the delivered dose of dialysis (area $Kt/V$) and the region of the country in which a patient was treated to account for geographic practice variations.

The analysis in which adjustment was made for delivered dialysis dose showed that the relative risk of death was decreased significantly by $\sim 25\%$ with the use of both substituted cellulose and synthetic membranes. After the added adjustment for geographic region, the decrease in the relative risk of death for the substituted cellulose and synthetic groups was still 20%. This investigative group corroborated these findings in a more recent analysis of patients dialysed during the same time period [19].

At the time these analyses were conducted, the vast majority of substituted cellulose dialysers used in the United States were of relatively low water permeability ($K_{\text{UF}} < 12 \ \text{ml/h/mmHg}$), with negligible usage of high-flux cellulose dialysers. On the other hand, the overwhelming majority of synthetic dialysers used at the time of the study were high-flux (predominantly polysulphone) with minimal usage of low-flux filters. Specifically, in the latter analysis [19], relatively low-permeability cellulose acetate accounted for $\sim 80\%$ of modified cellulose usage, while high-flux cellulose (i.e. cellulose triacetate) usage represented $<5\%$ of cellulose usage. Polysulphone represented $>95\%$ of the synthetic membrane usage, with the vast majority of utilization falling in the high-flux domain. Therefore, in the unsubstituted cellulose vs substituted cellulose comparison, dialyser flux was relatively invariant, such that mortality differences could be attributed reasonably confidently to differences in the membrane polymer (i.e. biocompatibility). For the unsubstituted cellulose vs synthetic comparison, membrane flux and biocompatibility were covariates such that the

Fig. 1. Pore size distribution and solute sieving coefficient profiles for three hypothetical dialysis membranes. The left diagram shows the number of pores as a function of mean pore size, while the right diagram shows the relationship between solute sieving coefficient and molecular weight. Reprinted with permission from Ronco et al. [6].
survival advantage conferred by the use of synthetic membranes may have been related to either (or both) of these parameters.

The potential role of membrane permeability (rather than membrane composition) was explored in a recent investigation in which the USRDS database from the same time period was employed. Using middle molecule clearance as a surrogate for dialyser flux, Leyboldt et al. [20] determined vitamin B\textsubscript{12} clearances for 19 different dialysers used in the treatment of the USRDS database patients. These clearances were estimated from the combination of blood and dialysate flow rates for a specific dialyser in conjunction with that dialyser’s manufacturer-derived vitamin B\textsubscript{12} KoA. This analysis suggested a significant inverse relationship between mortality and vitamin B\textsubscript{12} clearance. In fact, a 10% increase in the total vitamin B\textsubscript{12} clearance (per week) was associated with a significant 5% decrease in the risk of death. By comparison, a 0.1 increase in delivered urea Kt/V (per treatment) was associated with a 7% increase in the risk of death. These recent USRDS findings [18–20] suggest that, relative to low permeability unsubstituted cellulosic membranes, both enhanced biocompatibility (provided by modified cellulose and synthetic membranes) and higher permeability improve survival.

Over a study period extending from 1968 to 1994, Koda et al. [21] retrospectively assessed 819 patients treated either with a low-flux unsubstituted cellulosic dialyser or a high-flux dialyser. The latter group consisted of a number of different membranes, including PMMA, polysulphone, PAN and cellulose triacetate. For the last 6 years of the study, a dialysate ultrafilter designed to reduce the concentration of endotoxin and other bacterial products was used. The cellulosic group (n=571) consisted of patients treated solely with that type of membrane, while the high-flux group (n=248) included patients either treated solely with that type of membrane (n=63) or that had switched to that type of membrane (n=185). Patients treated either solely with or having switched to high-flux dialysis had an ~40% reduction in the relative risk of death compared with patients receiving conventional HD (P<0.05). In the high-flux group, membrane utilization was as follows: PMMA, 32%; cellulose triacetate, 29%; PAN, 17%; and polysulphone, 17%.

Finally, Woods and Nandakumar [22] recently attempted to isolate the effect of flux from membrane material in a retrospective analysis of 715 patients. These investigators compared the outcome of a group consisting of patients treated exclusively with low-flux polysulphone dialysers with a group treated for at least 3 months with a high-flux polysulphone dialyser. The general approach to dialyser prescription in this Singapore dialysis centre was to employ high-flux HD preferentially in patients with relatively greater comorbidity, including diabetic and elderly patients. Despite these differences in comorbidity unfavourable to the high-flux group, a Kaplan–Meier analysis suggested a significantly higher 5-year survival in this group (Figure 2). Interestingly, the significant divergence between the two curves did not appear to occur until after ~4 years of treatment. Cox proportional analysis, excluding diabetic patients, indicated a significant 65% decrease in the risk of death in the high-flux group relative to the low-flux cohort, while the same analysis including diabetics approached statistical significance (P=0.07).

Summary

An overview of membrane characteristics influencing dialyser performance has been provided. In addition, recent studies attempting to establish a relationship between membrane characteristics and survival of chronic HD patients have been reviewed. Emerging evidence from retrospective studies suggests that membrane flux is an important determinant of outcome in this patient population. A problem with some of these studies is the co-variation of membrane flux and composition. Data from prospective studies, such as those being performed currently in both Europe [23] and the US [24], should provide further elucidation.

References